Glycemic Index, Glycemic Load, and Carbohydrate Intake in Relation to Risk of Distal Colorectal Adenoma in Women

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Abstract

Case-control studies and a cohort study have shown inconsistent associations between a high glycemic index or a high glycemic load and risk of colorectal cancer. These dietary variables have not been examined in relation to risk of colorectal adenoma. We thus examined the associations between dietary glycemic index, glycemic load, and carbohydrate intake with risk of adenoma of the distal colon or rectum among 34,428 US women who were initially free of cancer or polyps, who completed a semi-quantitative food-frequency questionnaire in 1980, and who underwent endoscopy from 1980 through 1998. 1,715 adenoma cases (704 large adenomas, 894 small adenomas, 1,277 distal colon adenomas, and 504 rectal adenomas) were documented during 18 years of follow-up. Dietary glycemic index, glycemic load, and carbohydrate intake were not related to risk of total colorectal adenoma after adjustment for age and established risk factors [relative risk (RR) for extreme quintiles of glycemic index = 1.11, 95% confidence interval (CI) 0.94-1.32, *P* for trend = 0.66; RR for glycemic load = 0.92, 95% CI 0.76-1.11, *P* for trend = 0.63; RR for carbohydrate intake = 0.90, 95% CI 0.73-1.11, *P* for trend = 0.64]. In addition, no significant associations were found for large or small adenoma, distal colon or rectal adenoma, or across strata of body mass index. Our findings do not support the hypothesis that a high glycemic index diet, a high glycemic load diet, or high carbohydrate intake overall are associated with risk of colorectal adenoma. (Cancer Epidemiol Biomarkers Prev 2004;13(7):1192–8)

Introduction

Insulin and insulin-like growth factors (IGF) can stimulate proliferation and inhibit apoptosis of colorectal cells, and dietary patterns that exacerbate the insulin resistance syndrome may be associated with a higher risk of colon cancer (1, 2). High carbohydrate intake can adversely influence lipid and glucose metabolism, inducing hypertriglyceridemia, low high density lipoprotein cholesterol levels, high glucose levels, and hyperinsulinemia (3-5). Dietary glycemic index reflects the influence on blood glucose of a standard amount of carbohydrate from a specific food or diet, and the dietary glycemic load is an indicator of both the amount of carbohydrate and its glycemic index. Dietary glycemic index and dietary glycemic load seem to have increased in recent years because of increases in carbohydrate intake and changes in food processing (6). Epidemiologic evidence suggests that a diet with high glycemic load or high glycemic index may increase the risk of coronary heart disease (7) and type 2 diabetes (8, 9), especially in overweight and obese persons, who generally have insulin resistance.

More recently, the influence of hyperinsulinemia (1, 2) and abnormal glucose metabolism (10) on risk of colorectal cancer has drawn interest. In two case-control studies, persons who consumed diets with a high glycemic index and a high glycemic load were at elevated risk of colon cancer, especially if they were overweight (11, 12), but the relationship between glycemic load diet and risk of colorectal cancer was inconsistent in cohort studies (13, 14). However, the role of dietary carbohydrate amount and quality in relation to the risk of colorectal adenoma, the precursor of colorectal cancer, has not been studied. Furthermore, limited animal studies to date have not supported a role of high glycemic index diet in colon carcinogenesis (15, 16). Because of the limited and inconsistent data, we examined the hypothesis that a high glycemic index diet, a high glycemic load diet, and a high carbohydrate intake increase the risk of colorectal adenoma, particularly among women with a high body mass index (BMI).

Materials and Methods

Study Cohort. The Nurses' Health Study was initiated in 1976 when 121,700 female registered nurses in the United States ages 30 to 55 years completed a mailed questionnaire about their lifestyle factors and medical history. Every 2 years, a follow-up questionnaire was sent to these women so that information could be updated and newly diagnosed major illnesses identified. A food-frequency questionnaire was first administered in 1980. Deaths in the cohort were ascertained by reports from

Received 9/29/03; revised 2/23/04; accepted 3/15/04.

Grant support: Grants CA 55075 and CA 87969 from the NIH, Department of Health and Human Services.

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family members, the postal service, and a search of the National Death Index. We estimate that more than 98% of deaths were reported to us through these sources (17). The overall follow-up for this cohort was 96%. In this analysis, we included participants who returned the 1980 food-frequency questionnaire, and who had no diagnosis of cancer (excluding nonmelanoma skin cancer), inflammatory bowel disease, familial polyposis, or colorectal polyp before 1980. To reduce the potential for detection bias, we restricted the analysis to women who reported having undergone a colonoscopy or sigmoidoscopy between 1980 and 1998. More than 90% of the adenomas were diagnosed during endoscopic procedures for screening or for unrelated gastrointestinal conditions. Sigmoidoscopies do not examine proximal regions of the colon; thus, we analyzed only adenomas of the distal colorectum to prevent misclassification and potential detection bias. A total of 34,428 women met all the criteria for analysis. This study and analyses were approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard School of Public Health.

Ascertainment of Colorectal Adenoma. The ascertainment of adenoma cases and controls has been described previously (18). Briefly, we asked permission from women who reported a new diagnosis of polyp on the follow-up questionnaires to obtain pertinent medical records. Study investigators, blinded to the exposure information, reviewed the medical records to record the histologic type, the anatomic location, and size of reported polyps. We considered for analysis only cases of distal colorectal adenoma confirmed by histopathologic report (including carcinoma in situ), irrespective of whether or not they also had adenomas proximal to the descending colon or had hyperplastic polyps. Eligible for analysis was 1,715 distal colorectal, 1,277 distal colon, and 504 rectal adenoma cases from 1980 to 1998. Seven hundred four women were classified to have large adenomas (≥1 cm), and 894 as small adenomas; information on size was not available for 117 cases.

Dietary Assessment. In 1980, we collected information on usual diet using a semi-quantitative food-frequency questionnaire (19). For each of 61 food items assessed, a commonly used unit or portion size was specified, and each woman was asked how often, on average, during the previous year she had consumed that amount of the item. Nine responses were possible, ranging from ''almost never'' to ''six or more times per day.'' In 1984, a second dietary questionnaire, expanded to include 116 items, was administered. Similar dietary questionnaires were administered in 1986, 1990, and 1994. The average daily intake of nutrients was calculated by multiplying the frequency of consumption of each item by its nutrient content and summing the nutrient contributions of all foods. Methods used to assess the glycemic index of individual foods and mixed meals, as well as the measurement of dietary glycemic load in the Nurses' Health Study cohort, have been reported in detail elsewhere (7-9). We calculated dietary glycemic load by multiplying the carbohydrate content of each food by its glycemic index, and then adding the values from all foods. Dietary glycemic load thus represents the quality and quantity of carbohydrates and the interaction between the two (the product of glycemic index and carbohydrate intake indicates that a higher glycemic index has a greater effect at a higher carbohydrate intake). Each unit of dietary glycemic load represents the glycemic equivalent of 1 g carbohydrate from white bread. We also created a variable we termed overall dietary glycemic index by dividing the average daily glycemic load by the average daily carbohydrate intake. Red meat intake included beef, pork, or lamb as a main dish, beef in a sandwich, hamburger, hot dogs, bacon, and other processed meats, taking into account weight in grams of each portion size. Intakes of folate, vitamin D, and calcium included the sum of the frequency of consumption of specified portion sizes of those foods containing these nutrients and additionally intakes from multivitamins and specific supplements.

Statistical Analysis. The end point for this analysis was prevalence of distal colorectal adenoma at endoscopy. Controls consisted of women who did not have an adenoma of the distal colorectum at endoscopy. In additional analyses, we analyzed the adenomas by size because large adenomas (≥1 cm) may be more likely to reflect the influence of a tumor promoter, and also separately analyzed adenomas of the distal colon and rectum. Women were grouped into quintiles of dietary glycemic index, dietary glycemic load, and carbohydrate intake. In multivariate analysis, the relative risks (RR) estimated by the odds ratios were simultaneously adjusted for potential confounding variables by using multiple logistic regression. To best represent the participants' long-term dietary patterns during follow-up, we used a cumulative average method based on all available measurements of diet up to the beginning of each 2-year interval. Among women, dietary data from the 1980 questionnaire were used to predict colorectal adenoma diagnosed between June 1980 and June 1984; the average of the 1980 and 1984 dietary intake was used to predict outcomes between June 1984 and 1986; and so forth.

In the models, for covariates we included established and suspected risk factors as well as the indication for endoscopy. The covariates included age at endoscopy (5-year categories), indication for endoscopy, BMI (quintiles), pack-years smoked (non-smokers, tertiles of pack-years for smokers), alcohol consumption (10 g/d categories), family history of colon cancer, history of previous endoscopy, postmenopausal hormone use (premenopausal, never, current, past user), regular aspirin use, physical activity (quartiles), and quintiles of energy intake, energy-adjusted intakes of total fiber, vitamin D, calcium, folate, and red meat intake. To control for total energy intake, dietary glycemic index, dietary glycemic load, and other nutrients were adjusted for total energy intake by using the residual method (20). Tests for trend were conducted by assigning the median value to each quintile and modeling this value as a continuous variable. The log likelihood ratio test was used to assess the significance of interaction terms. We also conducted analyses stratified by BMI. We conducted all analyses using SAS version 6.11 (SAS Institute, Inc., Cary, NC).

Results

The prevalence of adenoma of the distal colon and rectum increased with age, BMI, higher prevalence of

Table 1. Characteristics of the study population

	Cases	Controls
Age at endoscopy (mean, y)	61.7	58.7
Smoking (mean, pack-years smoked)	17.6	12.2
Physical activity (mean, daily metabolic equivalents)	15.6	14.6
BMI (≥25 kg/m^2, %)	52.7	47.3
Family history of colorectal cancer (%)	33.6	22.4
Previous endoscopy before 1980 (%)	13.1	12.3
Current postmenopausal hormone use (%)	32.1	33.4
Aspirin use (≥2 times/wk, %)	21.9	25.4
Daily dietary intake		
Total energy (kcal)	1,683	1,683
Glycemic index	134.6	135.8
Glycemic load	74.3	74.3
Carbohydrate (%)	44.6	44.8
Protein (%)	18.8	18.8
Saturated fat (%)	12.9	13.0
Calcium (mg)	924.7	910.8
Vitamin D (IU)	318.4	326.1
Folate (μg)	392.1	401.5
Dietary fiber (g)	16.2	16.2
Beef, pork, or lamb as a main dish (servings/d)	1.2	1.2
Alcohol (g)	7.2	6.3

smoking and family history of colorectal cancer, and lower prevalence of aspirin use (Table 1). Dietary intakes, including glycemic index, glycemic load, and carbohydrate intake did not differ between cases and controls.

Table 2 shows the age-standardized baseline characteristics according to dietary glycemic index and glycemic load, grouped into quintiles. At baseline in 1980, women with high dietary glycemic index had a lower prevalence of smoking and vigorous physical activity, whereas women with high dietary glycemic load were slightly older and had a lower prevalence of smoking and previous endoscopy. BMI, family history of colon cancer, postmenopausal hormone use, and aspirin use did not differ according to glycemic index and glycemic load quintiles. Women with a high glycemic index diet consumed less protein, saturated fat, calcium, vitamin D, folate, total dietary fiber, and alcohol. However, women who consumed a high glycemic load diet had higher intakes of folate, total dietary fiber, and fiber from various sources, but had much lower alcohol consumption.

Dietary glycemic index was not appreciably related to risk of colorectal adenoma when adjusted only for age, or when also adjusted for dietary and non-dietary risk factors [RR for the highest versus the lowest quintiles of glycemic index = 1.11, 95% confidence interval (CI) 0.94-1.32, P for trend = 0.66 in multivariate; Table 3]. Dietary glycemic load and carbohydrate intake were related to lower risk of adenoma when adjusted only for age. However, after adjusting for dietary and non-dietary risk factors, these associations were not statistically significant (RR for the highest versus the lowest quintiles of glycemic load = 0.92, 95% CI 0.76-1.11, P for trend = 0.63; RR for the highest versus the lowest quintiles of carbohydrate intake = 0.90, 95% CI 0.73-1.11, P for trend = 0.64). In addition, we found no appreciable associations between dietary glycemic index, dietary glycemic load,

Table 2. Age-standardized baseline characteristics* according to quintiles of energy-adjusted dietary glycemic index and dietary glycemic load

	Quintiles of dietary glycemic index			Quintiles of dietary glycemic load		
	1 (lowest)	3	5 (highest)	1 (lowest)	3	5 (highest)
Mean	66.0	73.3	80.1	85.9	119.2	161.9
Age at endoscopy (y)	58.9	59.4	57.6	57.1	59.2	59.8
BMI (kg/m^2)	24.4	24.4	24.3	24.4	24.5	24.0
Smoking (pack-years smoked)	12.7	10.4	10.6	15.4	10.0	7.9
Vigorous exercise (%)†	54.0	47.1	37.4	46.3	46.5	45.0
Family history of colorectal cancer (%)	22.6	22.9	22.7	21.6	23.2	23.1
Previous endoscopy before 1980 (%)	14.3	10.7	13.2	16.1	11.4	10.8
Postmenopausal hormone use (%)	15.9	17.6	16.5	16.8	18.4	17.1
Any aspirin use (%)	48.2	48.2	47.3	48.4	48.2	46.5
Daily dietary intake						
Total energy (kcal)	1,554	1,590	1,521	1,562	1,592	1,533
Glycemic index	—	—	—	69.5	73.1	77.1
Glycemic load	101	120	144	—	—	—
Carbohydrate (g)	145	155	166	119	155	192
Total fat (g)	68.2	69.7	69.5	77.5	69.8	59.7
Protein (g)	84.6	76.5	69.1	82.5	77.7	68.4
Saturated fat (g)	28.0	27.9	27.3	31.5	28.0	23.5
Calcium (mg)	906	743	563	720	759	703
Vitamin D (IU)	358	299	237	282	296	303
Folate (μg)	429	378	317	355	369	392
Dietary fiber (g)	14.9	14.1	12.5	11.8	14.1	15.7
Cereal fiber (g)	2.0	2.6	3.0	1.9	2.6	3.0
Vegetable fiber (g)	5.8	5.0	4.2	4.8	5.0	5.1
Fruit fiber (g)	5.5	4.5	3.2	3.3	4.6	5.5
Beef, pork or lamb as a main dish (servings/d)	1.2	1.4	1.4	1.6	1.4	1.1
Alcohol (g)	8.9	6.5	4.5	12.8	5.5	2.6

*Included cases and controls.
†Sweat-producing exercise at least once per week.

Table 3. Relative risk for colorectal adenoma according to quintiles of dietary glycemic index, dietary glycemic load, and carbohydrate intake

	Quintiles of energy-adjusted dietary intake					
	1 (lowest)	2	3	4	5 (highest)	P_{trend}
Glycemic index						
Median	68.6	72.3	74.5	76.7	79.9	
Adenoma (n = 1,715)						
Age-adjusted	1	1.03 (0.89-1.20)	0.96 (0.82-1.12)	0.87 (0.75-1.02)	1.07 (0.92-1.25)	0.99
Multivariate*	1	1.09 (0.93-1.27)	1.01 (0.87-1.19)	0.92 (0.78-1.08)	1.11 (0.94-1.32)	0.66
Large (n = 704)						
Age-adjusted	1	0.98 (0.78-1.23)	0.92 (0.73-1.16)	0.84 (0.66-1.07)	1.00 (0.79-1.26)	0.60
Multivariate	1	1.04 (0.82-1.31)	0.97 (0.76-1.23)	0.88 (0.69-1.14)	1.01 (0.78-1.31)	0.73
Small (n = 894)						
Age-adjusted	1	1.14 (0.92-1.40)	1.01 (0.82-1.25)	0.96 (0.78-1.20)	1.18 (0.96-1.46)	0.38
Multivariate	1	1.18 (0.96-1.46)	1.07 (0.86-1.34)	1.01 (0.80-1.27)	1.26 (1.00-1.60)	0.18
Glycemic load						
Median	103.7	123.5	135.9	148.1	166.8	
Adenoma (n = 1,715)						
Age-adjusted	1	0.89 (0.76-1.03)	0.93 (0.80-1.09)	0.87 (0.75-1.02)	0.72 (0.61-0.84)	0.0001
Multivariate*	1	0.97 (0.82-1.14)	1.10 (0.93-1.30)	1.07 (0.89-1.27)	0.92 (0.76-1.11)	0.63
Large (n = 704)						
Age-adjusted	1	0.87 (0.69-1.09)	0.88 (0.70-1.11)	0.80 (0.64-1.02)	0.65 (0.51-0.83)	0.001
Multivariate	1	1.01 (0.79-1.30)	1.15 (0.89-1.48)	1.11 (0.85-1.46)	0.96 (0.71-1.29)	1.00
Small (n = 894)						
Age-adjusted	1	0.94 (0.76-1.16)	1.03 (0.84-1.27)	1.04 (0.85-1.28)	0.79 (0.63-0.99)	0.12
Multivariate	1	0.95 (0.76-1.19)	1.08 (0.86-1.36)	1.11 (0.87-1.41)	0.86 (0.66-1.12)	0.51
Carbohydrate intake						
Median (% of energy)	35.3	41.5	45.1	48.6	53.5	
Adenoma (n = 1,715)						
Age-adjusted	1	0.85 (0.73-0.99)	0.90 (0.78-1.05)	0.84 (0.72-0.98)	0.69 (0.59-0.81)	<0.0001
Multivariate*	1	0.91 (0.77-1.07)	1.04 (0.88-1.24)	1.03 (0.85-1.24)	0.90 (0.73-1.11)	0.64
Large (n = 704)						
Age-adjusted	1	0.79 (0.63-1.00)	0.77 (0.61-0.97)	0.79 (0.63-0.99)	0.61 (0.48-0.77)	0.0001
Multivariate	1	0.91 (0.71-1.17)	1.00 (0.77-1.31)	1.12 (0.84-1.48)	0.96 (0.70-1.32)	0.83
Small (n = 894)						
Age-adjusted	1	0.94 (0.75-1.16)	1.08 (0.88-1.33)	0.97 (0.79-1.20)	0.83 (0.66-1.03)	0.15
Multivariate	1	0.93 (0.73-1.17)	1.10 (0.87-1.40)	1.01 (0.78-1.31)	0.89 (0.67-1.18)	0.57

*Multivariate model included age, BMI, smoking, alcohol intake, family history of colon cancer, history of endoscopic screening or polyp diagnosis, year of endoscopy, aspirin use, menopausal status and postmenopausal hormone use, physical activity, energy intake, total fiber, red meat, folate, calcium, and vitamin D intake.

and carbohydrate intake and risks of large adenoma or small adenoma in multivariate analysis. Also, we found that dietary glycemic index, dietary glycemic load, and carbohydrate intake had no apparent relation to risk of distal colon or rectal adenoma when analyzed separately (Table 4). Furthermore, we conducted analyses from 1984 to 1998 beginning with the 1984 questionnaire, which was more detailed and could possibly capture glycemic index and glycemic load better than the 1980 questionnaire, but results did not differ (data not shown).

Because BMI is an important determinant of insulin resistance, we examined dietary glycemic index, dietary glycemic load, and carbohydrate intake in relation to adenoma risk by BMI category (Table 5). The dietary glycemic index, glycemic load, and carbohydrate intake had no clear relation to colorectal adenoma regardless of BMI (test of interaction for glycemic index, P = 0.77; for glycemic load, P = 0.53; and for carbohydrate intake, P = 0.33). We further examined the effects of dietary glycemic index, dietary glycemic load, and carbohydrate intake and BMI in relation to risks of large adenomas because BMI was a stronger risk factor for large adenomas than small adenomas in our cohort (test of interaction for glycemic index, P = 0.44; for glycemic load, P = 0.54; and for carbohydrate intake, P = 0.46) (21). Dietary glycemic index showed a slightly stronger association with risk of large adenomas than with total colorectal adenoma, but this was not statistically significant (RR for the highest quintiles of glycemic index and higher BMI = 1.24, 95% CI 0.87-1.78, P for trend = 0.48 as compared with the lowest quintiles of glycemic index and higher BMI). Similar, but weak associations were observed between high glycemic load or high carbohydrate intake and risk of large adenoma (RR for the highest quintiles of glycemic load and higher BMI = 1.09, 95% CI 0.72-1.65, P for trend = 0.37; RR for the highest quintiles of carbohydrate intake and higher BMI = 1.16, 95% CI 0.75-1.80, P for trend = 0.16). In previous reports from this cohort, alcohol consumption and physical activity have been related to risk of colorectal adenoma or colon cancer (21, 22); however, little relation between dietary glycemic index, dietary glycemic load, and carbohydrate intake and risk of colorectal adenoma was found across these strata (data not shown).

Discussion

Many studies have suggested that high carbohydrate intake has detrimental effects on lipid and glucose metabolism (3-6, 23, 24), and more recently these factors

Table 4. Relative risk for adenoma of the distal colon and rectum according to quintiles of dietary glycemic index, dietary glycemic load, and carbohydrate intake

	Quintiles of energy-adjusted dietary intake					
	1 (lowest)	2	3	4	5 (highest)	P_{trend}
Glycemic index						
Distal colon (n = 1,277)						
Age-adjusted	1	1.10 (0.92-1.31)	0.98 (0.82-1.17)	0.89 (0.74-1.07)	1.13 (0.95-1.35)	0.72
Multivariate*	1	1.15 (0.97-1.37)	1.04 (0.86-1.25)	0.94 (0.77-1.14)	1.20 (0.98-1.46)	0.36
Rectum (n = 504)						
Age-adjusted	1	0.90 (0.68-1.18)	0.99 (0.75-1.29)	0.87 (0.65-1.14)	0.93 (0.71-1.23)	0.57
Multivariate	1	0.94 (0.71-1.24)	1.03 (0.78-1.35)	0.88 (0.66-1.19)	0.90 (0.66-1.22)	0.47
Glycemic load						
Distal colon (n = 1,277)						
Age-adjusted	1	0.89 (0.74-1.06)	0.93 (0.78-1.11)	0.89 (0.74-1.06)	0.73 (0.61-0.88)	0.002
Multivariate*	1	0.98 (0.81-1.18)	1.10 (0.91-1.34)	1.09 (0.89-1.33)	0.95 (0.76-1.19)	0.96
Rectum (n = 504)						
Age-adjusted	1	0.93 (0.70-1.22)	1.03 (0.79-1.35)	0.91 (0.69-1.20)	0.76 (0.57-1.02)	0.08
Multivariate	1	0.96 (0.71-1.29)	1.12 (0.83-1.51)	1.02 (0.74-1.39)	0.85 (0.60-1.19)	0.44
Carbohydrate intake						
Distal colon (n = 1,277)						
Age-adjusted	1	0.82 (0.68-0.98)	0.91 (0.77-1.08)	0.82 (0.69-0.98)	0.69 (0.58-0.83)	0.002
Multivariate*	1	0.88 (0.72-1.06)	1.05 (0.86-1.28)	1.00 (0.80-1.24)	0.90 (0.71-1.15)	0.69
Rectum (n = 504)						
Age-adjusted	1	0.99 (0.75-1.30)	0.96 (0.73-1.27)	0.96 (0.73-1.27)	0.77 (0.58-1.04)	0.10
Multivariate	1	1.01 (0.75-1.36)	1.04 (0.76-1.43)	1.09 (0.78-1.52)	0.89 (0.61-1.30)	0.71

*Multivariate model included the variables listed in Table 3.

have been hypothesized to increase the risk of colorectal cancer (1, 2, 10). In our cohort studies, dietary glycemic index and dietary glycemic load have been related to coronary heart disease and type 2 diabetes (7-9). However, in this large prospective cohort of women, dietary glycemic index, dietary glycemic load, and carbohydrate intake were not associated with risk of distal colorectal adenoma, risk of large or small adenoma, and distal colon or rectal adenoma.

In a prospective study (13), dietary glycemic load was not associated with risk of colorectal cancer, consistent with the results of our study of adenoma, whereas dietary glycemic index and glycemic load have been shown to be associated with an elevated risk of colon cancer in case-control studies (11, 12). However, when analyzed separately by cancer site, dietary glycemic index was associated with increased risk of proximal tumors, but not distal tumors in one study (11). A risk

Table 5. Relative risk* of colorectal adenoma according to dietary glycemic index, dietary glycemic load, and carbohydrate intake stratified by BMI (kg/m^2)

	Quintiles of energy-adjusted dietary intake					
	1 (lowest)	2	3	4	5 (highest)	P_{trend}
Glycemic index						
Adenoma						
<25 kg/m^2 (n = 812)	1	1.08 (0.86-1.35)	1.13 (0.90-1.42)	0.80 (0.62-1.02)	1.10 (0.86-1.40)	0.90
≥25 kg/m^2 (n = 903)	1	1.09 (0.89-1.35)	0.92 (0.73-1.15)	1.03 (0.83-1.30)	1.14 (0.90-1.44)	0.47
Large adenoma						
<25 kg/m^2 (n = 328)	1	0.91 (0.64-1.28)	1.04 (0.74-1.46)	0.77 (0.53-1.11)	0.82 (0.56-1.19)	0.20
≥25 kg/m^2 (n = 376)	1	1.17 (0.85-1.61)	0.91 (0.65-1.29)	1.01 (0.71-1.43)	1.24 (0.87-1.78)	0.48
Glycemic load						
Adenoma						
<25 kg/m^2 (n = 812)	1	0.87 (0.69-1.10)	1.11 (0.88-1.41)	0.90 (0.70-1.17)	0.87 (0.66-1.13)	0.36
≥25 kg/m^2 (n = 903)	1	1.06 (0.85-1.34)	1.09 (0.86-1.38)	1.22 (0.96-1.56)	0.97 (0.74-1.27)	0.86
Large adenoma						
<25 kg/m^2 (n = 328)	1	1.00 (0.70-1.42)	1.21 (0.84-1.73)	0.88 (0.59-1.32)	0.82 (0.54-1.26)	0.32
≥25 kg/m^2 (n = 376)	1	1.03 (0.73-1.46)	1.10 (0.77-1.57)	1.32 (0.92-1.90)	1.09 (0.72-1.65)	0.37
Carbohydrate intake						
Adenoma						
<25 kg/m^2 (n = 812)	1	0.89 (0.71-1.13)	0.91 (0.71-1.18)	0.90 (0.68-1.18)	0.85 (0.63-1.14)	0.32
≥25 kg/m^2 (n = 903)	1	0.93 (0.73-1.17)	1.18 (0.92-1.50)	1.16 (0.89-1.50)	0.95 (0.71-1.28)	0.77
Large adenoma						
<25 kg/m^2 (n = 328)	1	0.92 (0.65-1.31)	0.89 (0.60-1.31)	0.80 (0.53-1.23)	0.77 (0.48-1.21)	0.22
≥25 kg/m^2 (n = 376)	1	0.90 (0.64-1.29)	1.12 (0.78-1.62)	1.44 (0.98-2.12)	1.16 (0.75-1.80)	0.16

*Multivariate model included the variables listed in Table 3, except for BMI.

limited to the proximal colon could account for our weak findings because we analyzed only adenomas of distal colon and rectum because sigmoidoscopies do not examine proximal regions of the colon. However, a prospective study of colon cancer showed a suggestive positive association in the distal colon but an inverse association in the proximal colon (13).

In various studies, the relationship between carbohydrate intake and risk of colorectal cancer and adenoma is fairly inconsistent; no significant associations were observed between carbohydrate intake and risk of colorectal cancer or adenomas in most studies (25-28), while one study showed that carbohydrate intake was inversely related to adenoma risk (29). One potential explanation is that dietary and non-dietary risk factors were not adequately adjusted for in some studies. Also, the primary sources of carbohydrate intake consumed by study population may differ; in some countries, the main sources of carbohydrate may be unrefined bread, whereas in others, it may be high glycemic index foods. Different sources of carbohydrates may vary in glycemic response and, therefore, may affect risk of colorectal cancer differently (30). In the New York University Women's Health Study (31) and cohort studies of Canadian women (13) and Hawaii Japanese men (32), carbohydrate intake was not associated with risk of colorectal cancer or colorectal adenomas, consistent with the results of our study. Also, carbohydrate intake was inversely related to risk of adenoma in the Health Professional Follow-up Study, although this relation was not statistically significant after adjustment for fiber intake (33).

Several aspects of glucose metabolism associated with high glycemic index and carbohydrate intake may theoretically influence colorectal carcinogenesis. A high carbohydrate intake induces hypertriglyceridemia and low high density lipoprotein levels (3-5, 24), and carbohydrate intake with high glycemic index can induce higher blood glucose levels (34, 35). Higher concentrations of glucose and triglyceride could influence growth of colorectal neoplasms (10). Serum triglyceride levels were associated with an increased risk of colorectal adenoma and cancer in several studies (36-39), whereas the Cardiovascular Health Study (40) reported no significant relationship. In addition, fasting or post-load plasma glucose levels were related to risk of colorectal cancer (40-45), but not to colorectal adenoma in two other studies (36, 37). However, in our study, dietary glycemic index, dietary glycemic load, and carbohydrate intake were not associated with risk of colorectal adenoma.

Alternatively, hyperinsulinemia has been proposed to increase risk of colorectal neoplasms (1, 2). Obesity and physical inactivity, the major modifiable determinants of insulin resistance or hyperinsulinemia (1, 2), have been associated with an elevated risk of colon cancer and advanced adenoma relatively consistently (21, 46-50). Women with high BMI ($\geq$25 kg/m^2) were also at an elevated risk of distal colon adenoma, especially large adenoma in our cohort (21). Clinical studies show that overweight individuals have a greater increase in insulin levels than leaner individuals after a high carbohydrate diet (55% of energy) (51), and Franceschi et al. (12) reported that the association between dietary glycemic load and colorectal cancer was much stronger among women with BMI $\geq$27 kg/m^2, suggesting that obesity amplified the adverse effect of high glycemic load. However, in our analyses stratified by BMI, high dietary glycemic index, glycemic load, and carbohydrate intake did not further increase risk of colorectal adenoma among women with high BMI ($\geq$25 kg/m^2).

Other factors may influence the effect of glycemic load and index on colorectal adenoma risk. In women, alcohol intake, a risk factor for colorectal adenoma, is inversely related to BMI, possibly by decreasing sugar consumption (22). Increased levels of leisure-time physical activity were inversely associated with risk of colon cancer (21, 52). Higher BMI also increased risk of colon cancer among women who were estrogen-positive (premenopausal women and postmenopausal women with hormone replacement therapy) in one study (53). However, no relation was found between dietary glycemic index, dietary glycemic load, and carbohydrate intake and risk of colorectal adenoma in stratified analyses of alcohol consumption, physical activity, and menopausal status (data not shown).

There are several major strengths of this study. The study was large and included 1,715 adenoma cases during 18 years of follow-up. Diet was assessed prospectively by detailed, validated, and repeated questionnaires, so dietary reporting was not influenced by knowledge of the existence of colorectal adenoma. In addition, many known or suspected risk factors for colorectal adenoma and colon cancer, including other dietary factors, BMI, smoking, physical activity, alcohol consumption, hormone use, and aspirin use were controlled. However, this study included prevalent adenoma, and some or many of the adenoma might have existed a long time before diet assessment. Therefore, we cannot rule out the possibility that diet information collected did not correspond to the etiologically relevant time for adenoma development or progression. Another limitation is that to avoid detection bias, the analysis excluded right-sided adenoma which would not be discovered on most sigmoidoscopic examinations, so our results may not be applied to the proximal colon.

In summary, our results do not support the hypothesis that high glycemic index diet or high glycemic load diet or carbohydrate intake increase risk of colorectal adenoma. Further studies need to focus on incidence of colorectal cancer, which reflects later stages of the disease.

Acknowledgments

We appreciate the contributions of Gary Chase, Karen Corsano, Lisa Dunn, Barbara Egan, and Mary Louie for their expert help.

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Cancer Epidemiol Biomarkers Prev 2004;13:1192-1198.